TOPIC IN REVIEW

Stem cell transplantation

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Stem cell transplantation is a generic term covering several different techniques (figure 1). For allogeneic transplants, hemopoietic stem cells are taken from the bone marrow, peripheral blood, or umbilical cord blood of a healthy donor matched for HLA type, who may be a family member or an unrelated volunteer. For autologous transplants, stem cells are taken from patients' own bone marrow or peripheral blood.

METHODS

Our review is based on current hematologic textbooks, review articles in major hematologic journals, and information from recent meetings of learned societies such as the American Society of Hematology and the European Bone Marrow Transplant Society. This review reflects our perspectives and is not meant to cover every likely use or possible advance in this rapidly expanding field.

STEM CELL TRANSPLANTATION TECHNIQUES

The first successful bone marrow transplantation in humans was performed between identical twins. With a greater understanding of the HLA system, it became possible to perform bone marrow transplantations between siblings who were HLA identical. Transplantation is widely used to treat congenital bone marrow disorders and malignant hematologic diseases. Today, more than 350 centers in Europe are performing over 18,000 transplantations a year. Centers may report their transplantations to the European Bone Marrow Transplant Registry, which periodically publishes outcome data. The European Bone Marrow Transplant Group is establishing a system of voluntary accreditation for transplantation centers, and most centers are likely to seek early accreditation.

DONOR AVAILABILITY

The major factor limiting the number of allogeneic transplantations performed is donor availability.

Sibling donors

We know from population-based studies that only 20% to 25% of patients eligible for allogeneic transplantation will have suitable sibling donors.[1]

Matched unrelated donors

To make transplantations available to a greater number of eligible patients, registries of volunteer bone marrow donors have been developed. These can provide transplant physicians with stem cells from unrelated but matched donors. More than 6 million donors are registered on national donor panels worldwide.

Transplants from unrelated volunteers are associated with higher morbidity and mortality than those from matched siblings, but outcomes are improving,[2] partly because modern molecular techniques allow closer matching of donors and recipients. Patients with chronic myeloid leukemia who are considered a good risk for transplantation (aged 20-40 years, seronegative for cytomegalovirus, in chronic phase, and receive a transplant within 1 year of diagnosis from a closely matched donor) have outcomes approaching those seen in allogeneic transplantations between siblings—that is, more than 70% survival at 5 years.[3]

Patients with common HLA types have a good chance of getting a match, unlike those with rarer HLA types, such as patients from ethnic minorities or those of mixed parentage. A suitable volunteer donor can take many months to locate, test, get the consent of, and pronounce medically fit, and delays may be critical in patients with acute leukemia. Their disease may relapse or progress before the search is completed, especially if a search has to be extended outside the country of residence.

Stem cells from umbilical cord blood

Cord blood from neonates contains substantial numbers of hemopoietic stem cells, which can be harvested at delivery, frozen, and then transplanted to patients who would not otherwise have a donor (figure 2).[4] Thousands of such donations are now stored in special banks worldwide, after cell counts and virologic screening tests are performed, and inventories of their HLA types are available to transplantation centers. Computer records can be scanned quickly, and donations can be matched with possible recipients without the delays inherent in securing an adult donor. The first cord blood transplantation was performed in 1989 by Gluckman and Broxmeyer, and since then more than 700 successful transplantations have been made. Such transplantations are associated with slightly delayed engraftment but a lower risk of graft-versus-host disease.[4] Cord blood transplants are usually reserved for children because the calculated stem cell dose in a donation often falls far short of the levels deemed necessary for stem cell engraftment in an adult.

Autologous transplantations

Autologous transplantation (patients are their own donors) is now the most common form of stem cell transplantation. Cryopreservation techniques now allow bone marrow to be stored safely and indefinitely, while the patient undergoes conditioning chemotherapy, without catastrophic loss of stem cells on thawing. Recovery of peripheral blood cell counts after cryopreserved marrow previously exposed to chemotherapy was transplanted was slow, and patients had prolonged neutropenia and thrombocytopenia. However, no graft-versus-host disease or prolonged immunosuppression developed, and the procedure was safer than with allogeneic transplants.

During the early 1980s, it was noted that marrow stem cells circulated in the peripheral blood, in small numbers in normal controls but in greater numbers in patients recovering from neutropenia induced by chemotherapy. Stem cell yields increased further if the patient was given bone marrow growth factors such as granulocyte colony-stimulating factor during the recovery period. In some patients, a large number of stem cells were found after treatment with the growth factor alone. With this technique, sufficient cells can usually be harvested from the peripheral blood over 2 to 3 days to safely perform an autologous transplantation. Patients receiving this type of transplant recovered their peripheral blood cell counts more rapidly than did patients receiving cryopreserved autologous bone marrow. Peripheral blood is now the preferred source of autologous stem cells for transplantation in adults.[5,6] In children, the choice of peripheral blood or marrow largely depends on the size of the child.

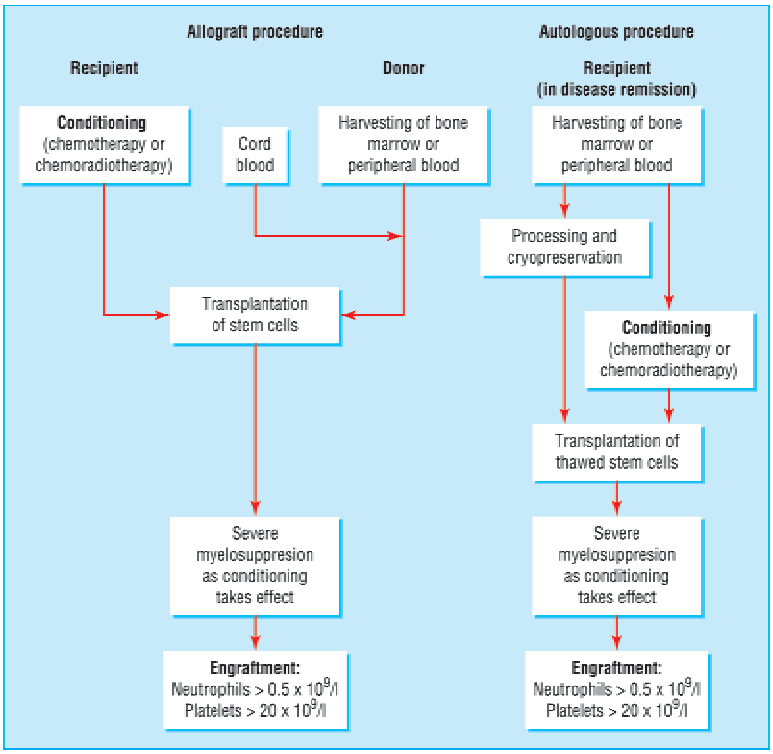

Figure 1 Stem cell transplantation techniques. Allogeneic transplantation was first used to treat congenital immune deficiencies, bone marrow failure, and hematologic malignant lesions and is now used routinely for some nonmalignant conditions such as thalassemia. Autologous transplantation was introduced to rescue the bone marrow of patients due to undergo high-dose chemotherapy, and it is now increasingly written into protocols for the primary treatment of solid tumors such as breast cancer and neuroblastoma. Autologous transplantation is also used experimentally to treat difficult autoimmune conditions such as systemic sclerosis and as a vehicle for gene therapy. Knowledge of stem cell transplantation techniques and their clinical application is therefore becoming essential for increasing numbers of medical specialists.

IMPROVING SAFETY AND EFFICACY OF STEM CELL TRANSPLANTATION

Stem cell transplantation is associated with substantial morbidity and (in allogeneic transplantation) mortality. Patients may spend considerable time in the hospital and need prolonged convalescence, especially if they are affected by graft-versus-host disease. However, several advances are associated with an improved outlook for patients and have led to increased interest in stem cell transplantation as a treatment.

Reduced-intensity conditioning for allografts

Conventional conditioning regimens for patients with leukemia are meant to ablate the patients' marrow and all traces of disease before infusion of donor stem cells. However, immunocompetent cells in the donation are widely recognized to also help clear recipients' residual tumor cells—a "graft-versus-tumor" effect[7,8]—and so completely eradicating the disease with conditioning may not always be necessary to achieve a cure. This observation led to experimentation with reduced-intensity protocols sometimes followed by immunotherapy (see below). Such nonmyeloablative transplantations are variously called minitransplants, low-intensity transplants, or "transplant-lite" conditioning. The use of peripheral blood as the source of the stem cells is associated with reduced toxic effects, morbidity, and mortality. These techniques are being introduced for older patients, who do not well tolerate conventional, high-intensity conditioning and transplantation. It remains to be seen how outcomes will compare with those of conventional approaches.

Donor lymphocyte infusions

If a malignant hemopoietic condition relapses after an allogeneic transplantation, lymphocyte infusions from the original donor can return the patient to remission by exploiting the graft-versus-tumor effect.[7,8] In chronic myeloid leukemia, such infusions can result in high rates of remission (60%-80%).[9] Unfortunately, response rates are lower in other diseases,[9] and treatment may be associated with the development of graft-versus-host disease.

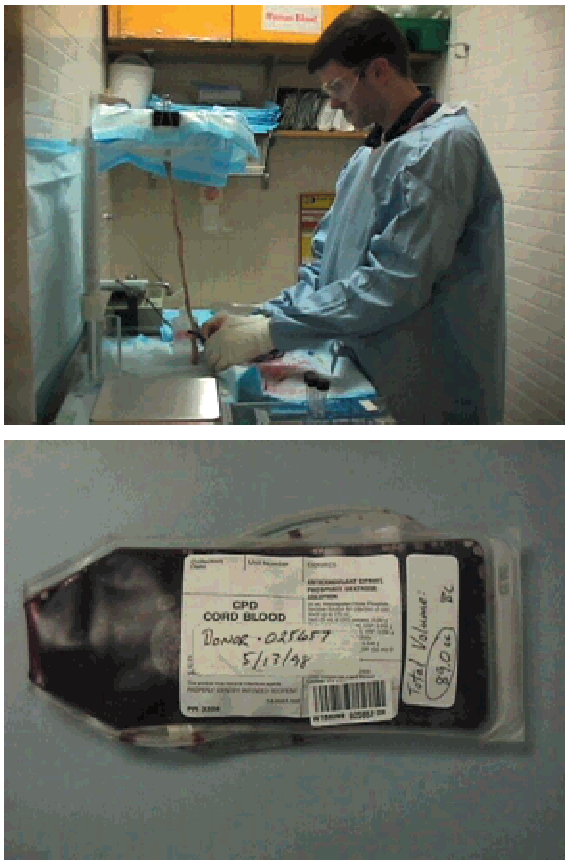

Figure 2 Harvesting of blood from umbilical cord. Photographs courtesy of Carolinas Cord Blood Bank, Duke University, Durham, NC.

IMPROVED HLA TYPING

The most important factor affecting the outcome of allogeneic transplantation is the quality of the HLA match between donor and recipient. New DNA-based techniques allow more sophisticated matching and are improving the outcome of this type of transplantation, particularly for unrelated transplants.

IMPROVED SUPPORTIVE CARE

Improvements in the supportive care of transplant patients have followed the development of bone marrow growth factors[10]; new antibiotic, antifungal, and antiviral agents; and better immunosuppressive treatments. In addition, we are able to detect infections earlier, with better tests for cytomegalovirus[11] and improved imaging techniques for fungal infections.[12]

Purging of transplants

An autograft may fail for 2 reasons. Either the chemotherapy fails to eradicate the tumor, leading to eventual relapse, or the graft may be contaminated with tumor cells, which are reinfused and again cause relapse. To reduce contamination with tumor cells, practitioners may attempt to clean up (purge) the transplant by using monoclonal antibodies directed against the tumor or by using peripheral blood stem cells instead of marrow. Recent studies, however, have shown that peripheral blood stem cell transplants are not necessarily less contaminated than marrow.[13]

INDICATIONS FOR STEM CELL TRANSPLANTATION

Indications for stem cell transplantation are constantly changing, partly because of the increasing safety of the procedure. The table shows established and possible indications and is a simplified version of the European bone marrow transplantation guidelines.[14] This list is not exhaustive but reflects the current practice of many clinicians performing transplantations.

Few randomized controlled trials provide level 3 evidence-based information for or against autologous stem cell transplantation. Such trials are notoriously difficult to perform because of problems in randomly allocating patients between treatment arms of radically different intensity. Exceptions include the Medical Research Council Acute Myeloid Leukaemia 10 trial,[15] in which the risk of relapse in the transplantation group was 37% compared with 58% in the nontransplantation group. The M D Anderson Breast Cancer Trial showed no advantage of autologous transplantation over high-dose chemotherapy,[16] whereas the Intergroupe Francais du Myelome trial in patients with multiple myeloma found improved response rates (81% vs 57%) and probability of event-free 5-year survival (28% vs 10%) in patients randomly allocated to receive autologous transplantation after conventional chemotherapy.[17] Results from the Scotland and Newcastle Lymphoma Group trial of autologous stem cell transplantation in patients with Hodgkin's disease[18] are currently being analyzed.

More commonly, stem cell transplantation is introduced into patient management because of failure to achieve satisfactory outcomes with standard treatments. Research groups may concentrate on a particular disease to establish the feasibility and outcome of stem cell transplantation. After results are published, some approaches are gradually incorporated into standard clinical practice.

Improvements in HLA matching, the treatment of graft-versus-host disease, and supportive therapy have enabled the wider application of allogeneic transplantation to more diseases, including some nonmalignant but severely debilitating conditions such as thalassemia and inherited metabolic disorders.[19] A greater understanding of permissible mismatches should allow a better choice of unrelated donor and further improve the outcome of unrelated donor transplantation.

Autologous stem cell transplantations allow the escala-

Indications for stem cell transplantation

Indication	Transplantations	
	Allogeneic	Autologous
Established uses	Severe aplastic anemia Chronic myeloid leukemia Acute myeloid leukemia in first complete remission*† Myelodysplasia† Acute lymphoblastic leukemia in first complete remission* Severe congenital immunodeficiency Acute myeloid leukemia and acute lymphoblastic leukemia in second complete remission Thalassemia	Acute lymphoblastic leukemia* Hodgkin's disease in second complete remission Non-Hodgkin's lymphoma in second complete remission Multiple myeloma Solid tumors such as neuroblastoma
Emerging uses	Multiple myeloma Sickle cell anemia Osteopetrosis Inherited metabolic disorders Hodgkin's disease Non-Hodgkin's lymphoma	Autoimmune disorders, such as systemic sclerosis Chronic lymphocytic leukemia Acute myeloid leukemia Solid tumors, such as breast, ovarian Chronic myeloid leukemia Hodgkin's disease in first complete remission Non-Hodgkin's lymphoma in first complete remission
Experimental uses	Chronic lymphocytic leukemia Renal cell carcinoma Breast cancer	Amyloidosis Other solid tumors Juvenile chronic arthritis

*Certain subtypes.
†Patient younger than 50 years

tion of cytotoxic treatments and reduce the period of neutropenia after treatment. They were introduced for patients with disorders in which higher doses of conventional chemotherapy might be expected to eradicate the disease—such as neuroblastoma,[20] non-Hodgkin's lymphoma, and Hodgkin's disease in second remission. Improved survival in patients in this last, difficult group[21] led to studies evaluating the merits of autologous transplantation for Hodgkin's disease in first remission and as a means of escalating treatment in solid tumors such as breast and ovarian cancers.

Autologous stem cell transplantation can also be used to "reeducate" the immune system of patients with some autoimmune diseases, such as systemic sclerosis,[22] or to introduce genetically or immunologically modified bone marrow.[23,24]

FUTURE DEVELOPMENTS

Improvements in harvesting techniques and the growth of stem cells in the laboratory (see box) will lead to increased safety of autografts and an expanding list of indications. Purging of stem cell transplants may become routine to reduce contamination with tumor cells.

Reducing the intensity of conditioning regimens for allografts will improve safety and increase applicability. Such transplantations may be followed by higher relapse rates, but these will be offset by the use of graft-versus-tumor effects by the infusion of donor lymphocytes. Techniques that offer a possibly higher cure rate than standard approaches will become suitable for many older patients with hematologic conditions and cancer. Improved immunosuppression protocols may allow transplantation across different HLA types.

Ongoing research programs with possible clinical applications include the development of vehicles for gene therapy, tumor-specific vaccines, and radionuclide conditioning agents.

Gene therapy

Worldwide, more than 300 phase I and II trials of gene therapy have now been undertaken or completed for cancer and monogenic disorders.[23,24] The possible value of such techniques is not in question, but the difficulties of achieving success in clinical settings should not be under-

Probable future developments

- Growth of stem cells in the laboratory, enabling wider use of cord blood donations in adults
- Improved techniques to "clean up" autologous stem cell transplants in cancer patients to prevent contamination with tumor cells
- Expansion of indications for transplantation, such as various solid tumors and severe autoimmune conditions
- Expansion of minitransplantation protocols—less intensive chemotherapy or chemoradiotherapy followed by planned infusions of donor lymphocytes as well as stem cells to "mop up" remaining tumor cells
- Increased use of donors not matched for HLA type

estimated; the major barrier is the inability of the inserted gene to reliably reach a sufficient number of target cells.

Tumor-specific vaccines

Tumor-specific vaccines to boost patients' immune response to their tumor are now entering clinical trials for non-Hodgkin's lymphoma.[25] More research is needed of the efficacy and optimal use of this immunotherapy.

Radionuclide-labeled conditioning agents

Radionuclide-labeled conditioning agents that have been bound to antibodies directed against stem cell antigens is an attempt to target conditioning radiotherapy to bone marrow cells so as to allow a higher dose of irradiation to the marrow with fewer systemic side effects.[26]

CONCLUSIONS

The next 5 to 10 years will be an exciting time for hematology. Currently, we have patients who might benefit from allogeneic transplant but who do not have a matched donor. The continued expansion of cord blood banks should alleviate this problem, especially if the banks can store donations from ethnic minorities in satisfactory numbers. The expansion of stem cell numbers from these small donations by their culture in the laboratory will, if successful, increase the number of allogeneic transplantations being performed and possibly increase the number of patients being cured.

In addition, we see closer collaboration with other medical specialists being necessary to assess the place of autologous transplantation in the treatment of more solid tumors and currently intractable autoimmune conditions.

For further reading, we recommend the guide to Internet resources for cancer at www.ncl.ac.uk/child-health/guides.

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